ARIC Manuscript Proposal #3854

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1.a. Full Title: Fatigue in Heart Failure: Predictors and Outcomes

b. Abbreviated Title (Length 26 characters): fatigue and heart failure outcomes

2. Writing Group:

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3. Timeline: Manuscript completed by January 2022

4. Rationale:

Heart failure affects an estimated 6.2 million adults in the United States[1] with a projected increase of 46% by the year 2030. It causes significant morbidity and mortality with nearly 80,000 heart failure-related deaths reported in 2016.[1] Fatigue is one of the most frequently reported symptoms of heart failure[2] causing significant patient distress.[3,4] Despite the widespread adoption of directed medical therapy, high symptom burden[5], mortality, and hospitalization as well as poor quality of life persist for patients with heart failure. [6,7,8] **Fatigue is a prevalent and distressing symptom for patients with heart failure and evidence suggests that it has implications for heart failure prognosis.** The presence of fatigue, and increased severity of fatigue has been associated with increased risk of hospitalization[9,10] and mortality[11,12]. Fatigue in heart failure is also associated with increased depression[3,4,13,14], poorer quality of life[15,16], worse self-care[17], and reduced physical[18,19,3], social[18], and emotional functioning.[20] However, fatigue in heart failure has largely been examined as a single experience and we do not yet understand the relationship between different types of fatigue and heart failure outcomes.

Fatigue in heart failure is divided into two, often co-occurring constructs that are important to the lived experience of heart failure patients: 1) generalized fatigue and 2) exertional dyspnea. Exertional dyspnea is characterized as shortness of breath related to activity or exertion. Exertional dyspnea is a symptom of exercise intolerance (or exertional fatigue) which is related to cardiac output, fluid volume overload, skeletal muscle function, and respiratory capacity.[21] It is generally associated with fluid congestion and disease progression/exacerbation which would trigger critical provider interventions such as medications, diagnostic testing, and/or hospitalization. General fatigue is a multi-dimensional, full-body experience not related to exertion. General fatigue is not clearly linked to fluid congestion, however, it is associated with depression which correlates with heart failure self-care.[22] Poorer self-care may lead to disease exacerbation and poorer heart failure outcomes.[23] **General fatigue and exertional dyspnea, though not mutually exclusive, are important to understand individually to intervene holistically and improve clinical and patient-reported outcomes.**

There are key gaps in the literature relating to fatigue in heart failure: 1) there is a lack of discrimination between general and exertional fatigue in spite of their known differences and **2)** there is little data separately examining outcome differences for general and exertional fatigue. **The purpose of this study is to 1) characterize the distribution of general and exertional dyspnea in the ARIC heart failure population and 2) quantify the relationship between these different types of fatigue and key heart failure outcomes**.

5. Main Hypothesis/Study Questions:

Aim 1: Characterize fatigue in heart failure as a latent variable. ***H1:*** *Utilizing latent class analysis or factor analysis (depending upon fit to the data), three distinct patterns of fatigue will be identified (general fatigue, exertional dyspnea, and their co-occurrence).*

Aim 2: Quantify the relationship between fatigue categories, either in latent classes, factors, (aim 1) or as cross-categorized individual measurement scales, with key heart failure outcomes (Primary: heart failure readmission and quality of life; Secondary: all-cause readmission, all-cause mortality). ***H2:*** *General fatigue and exertional dyspnea individually will each provide independent and complementary prognostic information and their co-occurrence will be associated with the worst heart failure outcomes.*

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: This study will be an analysis of visit 5 participants with a prior diagnosis of HF characterizing fatigue as a latent variable (in latent classes, factors, or individual measurement scales) and examining the prospective associations of general fatigue and exertional dyspnea with mortality and hospitalization as well as the cross-sectional associationswith quality of life.

Exposures: The exposure will be heart failure fatigue, as determined through either latent class analysis or factor analysis (depending upon the appropriateness of the method). We have selected items from scales collected at visit #5 that conceptually reflect either general fatigue or exertional dyspnea to be used in the latent class analysis or factor analysis. These items are shown here in table 1.

Latent Class Analysis:

We will perform latent class analysis using responses from scale items shown in table 1 collected from visit 5. We hypothesize that there will be 2-3 unique latent classes representing the predominance of general fatigue, exertional dyspnea, or their co-occurrence, respectively. If latent class analysis is not an appropriate method, then we will proceed with a factor analysis utilizing the same items in table 1.

Factor Analysis:

If latent class analysis is not an appropriate method, then we will use factor analysis with principle component analysis and iterated principle factoring methods. Individual participants' factor membership will be determined based on an individuals' factor score which will determine the predominance of either type of fatigue, or their co-occurrence. If this method is also not appropriate, then we will use a cross-categorization method with psychometrically validated scales for general and exertional fatigue.

Cross-Categorization Method:

If latent class analysis and factor analysis both not appropriate methods, then we will categorize individuals into one of three groups based on their predominating symptom: 1) general fatigue; 2) exertional dyspnea; 3) the co-occurrence of general fatigue and exertional dyspnea and 4) the absence of both types of fatigue. General fatigue will be defined using the 2 somatic symptom items from the CES-D depression questionnaire (see table 1). In the absence of a validated measure of general fatigue in the ARIC dataset at visit 5, the two somatic items of the CES-D scale will be used. These items have previously been validated to measure the somatic symptoms of depression (fatigue and loss of energy).[24] General fatigue will be scored dichotomously (presence or absence). General fatigue will be classified as "present" if the participant answers a 2 or a 3 on either of the CES-D items 3 or 11. This definition comes from the ARIC derived variable EXAUSTCOMP which was designed to measure fatigue/energy level in frailty. Exertional dyspnea will be measured on an ordinal scale using the RSE questionnaire for respiratory symptoms. The RSE is adapted from the MRC breathlessness scale, which is psychometrically validated for the measurement of dyspnea on exertion.[25] We will define three dyspnea groups based on scores from the RSE questionnaire: 1) no exertional dyspnea (score=1), 2) moderate exertional dyspnea (score = 2-3), and 3) severe exertional dyspnea (score $\geq$ 4). Figure 1 is an example of how cross-categorization will be performed:

Figure 1. Fatigue Cross-Categorization

General Fatigue	**Exertional Dyspnea**		
	None	Moderate	Severe
Yes			
No			

Table 1. Items selected for latent class analysis or factor analysis

Hypothesized Fatigue Class	Scale/Item	Item Question	Item Response Scale
General Fatigue	CES-D item 3	During the past week… I felt everything I did was an effort	1 = Hardly ever or never (<1 day in the last week) 2 = Some of the time (1-2 days in the past week) 3 = Much or most of the time (3-7 days in the past week)
	CES-D item 11	During the past week… I could not get "going"	1 = Hardly ever or never (<1 day in the last week) 2 = Some of the time (1-2 days in the past week) 3 = Much or most of the time (3-7 days in the past week)
	NHX item 12	Are you sleepy most of the day?	Yes/no
	NHX item 13	In the past month, how many days did you "doze off" during the day other than taking a regular nap?	>or= 4days per month (1 day per week) < 4 days per month (1 day per week)
	DCF item 10	Are you sleepy every day?	Yes/no
Exertional Dyspnea	RSE item 6	Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	Yes = 1 No = 0
	RSE item 7	Do you have to walk slower than people of your age on the level because of breathlessness?	Yes = 1 No = 0
	RSE item 8	Do you ever have to stop for breath when walking at your own pace on the level?	Yes = 1 No = 0
	RSE item 9	Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level?	Yes = 1 No = 0
	RSE item 10	Are you too breathless to leave the house or breathless on dressing or undressing?	Yes = 1 No = 0

Legend: RSE – Respiratory Symptom Questionnaire, CES-D – Center for Epidemiologic Studies Depression Scale, NHX – Neurological History, DCF – NCS Diagnostic Classification Form

Outcomes: Heart failure readmission, all-cause readmission, and mortality, as well as quality of life will be the outcomes of interest. All clinical longitudinal outcomes (mortality, heart failure hospitalization, all-cause hospitalization) will be collected through 2018 (or the most recent follow-up available). Quality of life will be assessed cross-sectionally at visit 5. Quality of life will be measured using the SF-12 scale which has been validated to measure health-related quality of life in a diversity of populations.[26,27]

Inclusion criteria: Prior diagnosis of heart failure and participation in exam #5. Diagnosis of heart failure will be defined using the ARIC derived variables: 1) prevhf52 (n=907) and 2) prevdefposshf51 (n=1114). We will perform separate analyses for each definition. The derived variable "prevhf52" is defined as visit 5 prevalent heart failure based on the HFRC Recommended definition as of 2018. The derived variable "prevdefposshf51" is defined as visit 5 definite or possible heart failure for closed event years.

Exclusion criteria: Diagnosis of cancer, individuals with missing fatigue data at visit 5, and the small number of individuals that are non-black or non-white.

Covariates: In all analyses, we will adjust for age, race, sex, BMI, smoking status, drinking status, hypertension, diabetes, total cholesterol, concurrent respiratory conditions and the use of beta-blockers and diuretics in the last 4 weeks. Depending upon statistical power, we will also consider adjusting for the co-occurrence of frailty.

Summary of Data Analysis:

- Exploratory data analysis will be performed, and data will be described using means and standard deviations or medians and IQR (continuous variables) depending upon data distributions. Categorical or dichotomous variables will be described with percentages and frequency counts. Data will be evaluated for data distributions, skewedness, and missing data. Alpha will be set at 0.05 and all inference tests will be two-sided.
- We will perform latent class analysis using the MPlus software with the survey items identified in table 1. Latent classes will be selected utilizing model estimation parameters including BIC and bootstrap likelihood ratio tests.
- If latent class analysis is not an appropriate method, then we will use factor analysis with principle component analysis, iterated principle factoring estimation, and promax (oblique) rotation methods. Individual participants' factor membership will be determined based on an individuals' factor score which will determine the predominance of general fatigue, exertional dyspnea, or their co-occurrence. If this method is also not appropriate, then we will use a cross-categorization approach using psychometrically validated scales to score general fatigue and exertional dyspnea (described in "exposures" section).
- We will compare baseline characteristics across fatigue classes (or factors or cross-categories) using independent t-test, chi squared test, and ANOVA for >2 group comparisons.
- We will perform multivariable cox proportional hazards regression to test the relationship between fatigue classes, factors, or cross-categorizations of general fatigue and exertional dyspnea with heart failure hospitalization, all-cause hospitalization, and mortality. We will perform multivariable linear regression to determine the cross-sectional relationship between fatigue classes (aim 1) or cross-categorizations of general fatigue and exertional dyspnea and the outcome of quality of life.
    - We will explore whether prognostic implications based on fatigue type differ between those with HFrEF versus HFpEF. To perform this, we will stratify our previous analysis on heart failure phenotype. This will be an exploratory analysis due to the limitations of statistical power because of the smaller proportion of individuals at visit 5 with HFrEF and our given sample size.

Sensitivity Analyses:

- We will repeat the analyses above excluding individuals with comorbid COPD or other respiratory conditions. These analyses may be limited by power due to the number of individuals who would need to be excluded due to the presence of a respiratory condition.
- We will perform additional sensitivity analyses excluding those with a confirmed diagnosis of depression at visit 5.
- prevhf52 (n=907) and prevdefposshf51 (n=1114) will be used as our primary definitions of heart failure diagnosis. However, we will perform a sensitivity analys using prevdefhf51 (n=355) as our definition because it is the most specific definition. We will perform a sensititivity analysis stratifying individuals on whether or not they had an ADHF hospitalization in the past year before visit 5, although we will have limited statistical power due to sample size.

Limitations:

- Risk of residual confounding due to the observational nature of the study
- Lack of identification of latent classes of fatigue using latent class analysis. We will address this by utilizing factor analysis as another statistical method for identifying symptom groups. If factor analysis is also not an appropriate method, then we will cross-categorize individuals based on their scale scoring into different fatigue groups.
- Utilizing groups of survey items that have not be psychometrically validated to measure the different types of fatigue in the latent class analysis and/or factor analysis. This is a limitation of utilizing a dataset that has not collected exactly what would be required to more precisely measure the symptom of interest. The results of this study would need to be validated with additional, prospective data collection in future research.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes ___X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes ___X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

- ARIC Manuscript Proposal #2852 - Hospital readmissions for patients hospitalized with acute decompensated heart failure and preserved vs. reduced ejection fraction
- ARIC Manuscript Proposal #2293 - Outcomes and Healthcare Utilization of Heart Failure Stages in the ARIC Cohort
- ARIC Manuscript Proposal # 1276 - Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study
- ARIC Manuscrip Proposal #2317 - Prognostic importance of dyspnea in the community: The ARIC study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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